

This Page Is Inserted by IFW Operations
and is not a part of the Official Record

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

**As rescanning documents *will not* correct images,
please do not report the images to the
Image Problem Mailbox.**

MIGRAINE MEDICINE AND METHOD FOR TREATING SAME WITHOUT
CAFFEINE

5 This application claims priority as a divisional application of U.S. non-provisional patent application serial no. 09/593,238 (filed on June 14, 2000) which relies on the priority of provisional patent application Serial Number 60/144,973 which was filed on July 22, 1999.

FIELD OF THE INVENTION

10 The present invention relates generally to compositions and methods used to alleviate the symptoms and pain associated with an acute migraine attack.

BACKGROUND OF THE INVENTION

15 An estimated 24 to 26 million Americans--about 18% of women and 6% of men--suffer from migraine pain and migraine-related symptoms. (Stewart WF, Lipton RB, Celetano DD, Reed ML. Prevalence of migraine headache in the United States: relation to age, income, race, and other sociodemographic factors. JAMA 1992; 267:64-69.)
20 Attacks are common, with more than 32% of sufferers experiencing more than four episodes per month. (Rasmussen BK, Stewart WF. The Epidemiology of Migraine. In: Olesen J, Tfelt-Hansen P, Welch KMA, editors. The Headaches, second edition, New York, N.Y.: Raven Press; 2000; p. 227-233.)
25

Migraine, a heterogeneous disorder, produces a wide spectrum of pain and associated disabilities, both within and among individual sufferers. The spectrum includes mild pain and no disability in approximately 5-

15% of migraine attacks, moderate to severe pain and disability in approximately 60-70% of attacks, and incapacitating pain and total disability in the remaining approximately 25-35% of attacks. (Stewart WF, 5 Schechter A, Lipton RB. Migraine heterogeneity: disability, pain intensity, and attack frequency and duration. Neurology 1994; 44 Suppl 4:S24-S39 and Lipton RB, Stewart WF. Migraine in the United States: A review of epidemiology and health care use. Neurology 1993; 43 10 Suppl 3:S6-S10.)

Recent population-based epidemiological studies in the United States and elsewhere, have found that most people with migraines are not currently consulting a physician for their migraine attacks, and only about 15 one-third have ever been diagnosed by a doctor. (Edmeads J. Findlay H, Tugwell P, Pryse-Phillips W, Nelson RF, Murray TJ. Impact for migraine and tension-type headache on lifestyle, consulting behavior and medication use: a Canadian population survey. Can J 20 Neurol Sci. 1993; 20:131-137; Lipton RB, Stewart WF. Medical consultation for migraine [abstract]. Neurology 1994; 44 Suppl 2:A199; and Rasmussen BK, Jensen R, Olesen J, Impact of migraine on sickness, absence and utilization of medical services: a Danish population 25 study. J Epidemiol Community Health 1992; 46:443-446.) The overwhelming majority (95% of men and 97% of women) of migraineurs, i.e., individuals who suffer from migraines, used medication to assuage their pain, although only about 28% of the men and 40% of the women 30 have ever used prescription medications. (Lipton RB, Stewart WF, Celentano DD, Reed ML. Undiagnosed migraine: A comparison of symptom-based and physician diagnosis.

Arch Int Med 1992; 152:1273-1278; and Celentano DD, Stewart WF, Lipton RB, Reed ML. Medication use and disability among migraineurs: a national probability sample survey. Headache 1992; 32:223-228.) More than
5 90% of migraineurs use nonprescription medication for their migraines and the majority use nonprescription medications exclusively. (Stang PE, Osterhaus JT, Celentano DD. Migraine: patterns of healthcare use. Neurology 1994; 44 Suppl 4:S47-S55; and Edmeads J,
10 Findlay H, Tugwell P, Pryse-Phillips W, Nelson RF, Murray TJ. Impact for migraine and tension-type headache on lifestyle, consulting behavior and medication use: a Canadian population survey. Can J Neurol Sci. 1993; 20:131-137.)

15 Many migraine sufferers use single-agent nonprescription analgesics such as acetaminophen, or aspirin, or non-steroidal anti-inflammatory agents to treat their attacks. (Lipton RB, Newman LC, Solomon S. Over-the-counter medication and the treatment of
20 migraine. Headache 1994; 34:547-548.) In other countries, a number of nonprescription drugs are specifically approved for migraine pain. (Lipton RB, Newman LC, Solomon S. Over-the-counter medication and the treatment of migraine. Headache 1994; 34:547-548.)
25 The effectiveness of self-treatment of a migraine and the effectiveness of most such nonprescription drugs in relieving or aborting migraine pain and/or the characteristic symptoms of a migraine has not been adequately studied in well-controlled clinical trials.
30 (Lipton RB, Newman LC, Solomon S. Over-the-counter medication and the treatment of migraine. Headache 1994; 34:547-548.) Acetaminophen, aspirin, and caffeine are

approved for relief of nonspecific headaches and tension headaches (Migliardi JR, Armellino JJ, Friedman M, Gillings DB, Beaver WT. Caffeine as an analgesic adjuvant in tension headache. Clin Pharmacol Ther 1994; 56:576-586), which are clinical and physiologically distinct from a migraine.

Caffeine is widely consumed and has also been indicated for use to treat asthma, drowsiness, fatigue, lumbar puncture headache, and neonatal apnea. Caffeine is also an analgesic adjuvant for a variety of pain conditions and has been included in combination with other analgesics, ergot alkaloids, and barbiturates in prescription formulations for a migraine. (Laska EM, Sunshine A, Mueller F, Elvers WB, Siegel C, Rubin A. Caffeine as an analgesic adjuvant. JAMA 1984; 251:1711-1718; Olesen J. A review of current drugs for migraine. J Neurology 1991; 238 Suppl 1:S23-S27; Solomon GD. Therapeutic advances in migraine. J Clin Pharmacol 1993; 33:200-209; and Sawynok J. Pharmacological rationale for the clinical use of Caffeine. Drugs 1995; 49:37-50.) Caffeine itself may act to relieve a migraine. Caffeine has shown to reduce cerebral blood flow in humans and to be a nonselective adenosine receptor antagonist. Reduction of cerebral blood flow may be due to caffeine inhibition of the adenosine A2 receptor. (Sawynok J. Pharmacological rationale for the clinical use of Caffeine. Drugs 1995; 49:37-50.) A2 receptors are on cerebral vascular muscles, and act to cause vasodilation. Hence, their inhibition would have the effect of vasoconstriction similar to other medications used to abort the migraine headache.

Although the symptom pattern varies among migraine sufferers, the severity of migraine pain justifies a need for vigorous therapy in the great majority of cases. Traditional therapy, such as ergotamine, although effective during the prodrome phase of a migraine attack, is known to become progressively less effective if its administration is delayed. Ergotamine is frequently combined with caffeine, a known analgesic adjuvant, to facilitate absorption of the ergot alkaloid. (Schmidt R, Fanchamps A. Effect of Caffeine on intestinal absorption of ergotamine in man. Eur J Clin Pharmacol 1974; 57:213-216.) However, repeated dosing of ergotamine induces long-lasting and cumulative vasoconstriction, thereby requiring careful instructions and management of individuals who take oral preparations for migraine attack.

Because of the cumulative toxicity of ergotamine and its derivatives, safer therapeutics for the treatment and prophylaxis of migraines have been sought. Examples of such ergotamine alternatives are ergonovine, propranolol, and methysergide. Significant toxicity, however, also occurs in nearly 40% of the individuals who take these agents. A prescription anti-migraine medication that is an alternative to ergotamine and its derivatives is sumatriptan (or sumatriptan succinate), which is a selective 5-hydroxytryptamine. (Deleu D, Hanssens Y, Worthing E. Symptomatic and prophylactic treatment of migraine: a critical reappraisal. Clin Neuropharmacol 1998; 21(5):267-279; and Stewart WF, Lipton RB, Celentano DD, Reed ML. Prevalence of migraine headache in the United States: relation to age, income, race, and other sociodemographic factors. JAMA 1992;

267:64-69.) When given early, anti-migraine medications effectively abort the acute symptoms of a migraine attack and the prodrome symptoms. Most of these medications, such as ergotamine, its derivatives, and selective 5-hydroxytryptamine agonists, share the physiological property of causing vasoconstriction. (Deleu D, Hanssens Y, Worthing E. Symptomatic and prophylactic treatment of migraine: a critical reappraisal. Clin Neuropharmacol 1998; 21(5):267-279.)

10 Thus, a clear goal in the art is to discover new, safe, nontoxic, and effective anti-migraine drugs and treatments, particularly nonprescription treatment medications that can be self-administered without the need of a medical prescription.

15 SUMMARY OF THE INVENTION

 The present invention relates to a medicinal composition for treating individuals afflicted with pre-migraine conditions, migraine-associated symptoms, and/or migraine pain of mild to severe intensity. The medicinal composition comprises at least pseudoephedrine and acetaminophen and is orally administered.

 DETAILED DESCRIPTION OF THE PRESENT INVENTION

 In general, the migraine condition, with or without aura, has a variety of characteristic features. Migraine attacks are episodic and self-limited. The duration of untreated or unsuccessfully treated migraine attacks can be from several hours to several days (e.g., about four hours to about three days). Common pain characteristics of migraines include pain in a unilateral location, with a pulsating quality. Pain is

usually of moderate to severe intensity and is aggravated by routine physical activity. One or more of a cluster of symptoms is recognized to frequently accompany migraines, namely, nausea and/or vomiting, photophobia, phonophobia, and functional disability, i.e., difficulty in performing routine work-related and non-work-related tasks.

The prodrome phase of a condition of migraine occurs before aura and before severe or throbbing migraine pain. Frequently during prodrome, the migraine sufferer experiences mood changes, lethargy, and tiredness. It will also be appreciated that migrainous aura, which is experienced by about 20% of migraine sufferers, precedes severe migraine pain and throbbing. Aura involves distinctive auditory and visual distortions, which may involve visual scotomas or even hemianopia and speech abnormalities, which develop prior to severe migraine pain and throbbing.

Medicinal treatment of migraine condition can be done during the prodrome phase, or in the aura phase (when it occurs), which are known to precede an acute migraine attack and migraine pain. Generally, the acute medicinal treatment is more effective in the prodrome phase. However, most acute medicinal treatments for migraine such as the present invention can be administered during the prodrome to abort the migraine attack or during the migraine attack once the migraine pain and its other symptoms have developed in order to reduce or eliminate migraine pain and its associated symptoms.

As stated above, the present invention relates to a medicinal composition for treating individuals afflicted with pre-migraine conditions, migraine-associated symptoms, and/or migraine pain of mild to severe intensity. The medicinal composition comprises at least pseudoephedrine and acetaminophen and is orally administrated. Each component of this medicinal composition must be shown to be safe and useful in treating the migraine complex, and evidence shows that the ingredients of the combination can work synergistically to treat a migraine. For example, one additional component that can be added to the medicinal composition which adds synergistic effect is caffeine.

The ingredients of the combination medication of pseudoephedrine, acetaminophen, and caffeine act synergistically. Caffeine has been shown to act synergistically with acetaminophen to produce analgesia, (Sawynok J. Pharmacological rationale for the clinical use of Caffeine. Drugs 1995; 49:36-50.) and to enhance the action of other medications such as ergotamine in relieving acute migraine attacks by increasing its absorption. (Schmidt R, Fanchamps A. Effect of Caffeine on intestinal absorption of ergotamine in man. Eur J Clin Pharmacol 1974; 57:213-216.)

As stated previously, caffeine itself may act to relieve the migraine. Caffeine has shown to reduce cerebral blood flow in humans and to be a nonselective adenosine receptor antagonist. Reduction of cerebral blood flow may be due to caffeine inhibition of the adenosine A2 receptor. (Sawynok J. Pharmacological rationale for the clinical use of Caffeine. Drugs 1995;

49:37-50.) A2 receptors are on cerebral vascular
muscles, and act to cause vasodilation. Hence, their
inhibition would have the effect of vasoconstriction
similar to other medications used to abort the migraine
headache.

The large arteries at the base of the brain and the
pia mater arteries make up the innervated vascular
system of the cerebral vessels, which has a rich
adrenergic nerve supply and responds to catecholamines.
These vessels would vasoconstrict in response to
sympathomimetic drugs such as pseudoephedrine. The non-
innervated vascular system is connected serially to the
first, consisting of parenchymal arteries and terminal
high resistance arterioles. The newer theories about
pathogenesis of migraine complex describe that in
susceptible individuals trigger factors set off a series
of local and systemic events that initiate both focal
and generalized manifestation of the migraine.
Generally, an initial vasoconstriction phase occurs
locally and predominantly in the unilateral cerebral
vessels. This unilateral vasoconstriction is associated
with aura in cases of a classic migraine. The
vasoconstriction is followed by reflex vasodilation due
to local anoxia, acidosis, and systemic drop in
serotonin. Marked vasodilation with accumulated
vasoactive substances sensitizes the pain receptors in
the blood vessels and produces a sterile inflammation.
These changes along with the vasodilation cause the pain
in migraine. (Seymour D. Head Pain Diagnosis and
Management. Clin Symp 1994; 46(3):2-34.)

Abortion of a migraine headache is thought to be achieved by vasoconstriction of dilated intracranial and extracranial vessels since vasodilation is associated with the headache phase. (Seymour D. Head Pain
5 Diagnosis and Management. Clin Symp 1994; 46(3):2-34.;
Godsby PJ. Mechanism and management of headache. J R
Coll Physicians Lond May/June 1999; 33(3):228-234; and
Sawynok J. Pharmacological rationale for the clinical
use of Caffeine. Drugs 1995; 49:37-50.)
10 Vasoconstriction produces reduction in blood flow. For
example ergotamine and sumatriptan produce
vasoconstriction of cranial blood vessels. (Deleu D,
Hanssens Y, Worthing E. Symptomatic and prophylactic
treatment of migraine: a critical reappraisal. Clin
15 Neuropharmacol 1998; 21(5):267-279.) The termination of
the headache is achieved 1) by restoring the loss of
homeostasis of blood supply to the brain to reduce the
sterile inflammation caused by vasodilation and 2) by
reducing the vasodilated vessels closer to a normal
20 state that would directly decrease the sensation of pain
in the innervated vessels.

Caffeine and pseudoephedrine may have a synergistic
affect on cerebral vasoconstriction, since
pseudoephedrine acts as an agonist directly on both
25 alpha and, to the lesser degree, beta-adrenergic
receptors. Activation of alpha-adrenergic receptors on
vascular smooth muscles causes vasoconstriction.
(Seymour D. Head Pain Diagnosis and Management. Clin
Symp 1994; 46(3):2-34.)

30 Acetaminophen has been routinely used to treat mild
to moderate migraines. (Godsby PJ. Mechanism and

management of headache. J R Coll Physicians Lond
May/June 1999; 33(3):228-234; and Deleu D, Hanssens Y,
Worthing E. Symptomatic and prophylactic treatment of
migraine: a critical reappraisal. Clin Neuropharmacol
1998; 21(5):267-279.)

Turning to the present invention and study, a hand
full of migraine patients were treated privately with
the combination of pseudoephedrine 60 mg and
acetaminophen 1000 mg every six (6) hours. These
patients reported a reduction of their migraine symptoms
such as headache, nausea, phonophobia, and photophobia
in 2 hours after treatment, as compared to acetaminophen
alone. Most cases of migraine attack were completely
aborted after one or two treatments (see Table 1).

Table 1

Age	Sex	Severity of headache on a scale of 1-10, before the medication	Severity of headache on a scale of 1-10, after the medication	Other symptoms besides headache	Relief of other symptoms achieved
29	F	8	Completely relieved	Photo and Phono	All relieved
34	M	6	Completely relieved	Photo, nausea, and Phono	All relieved
31	F	9.5	Completely relieved	Photo, nausea, and Phono	All relieved

Notes on Table 1:

Age is given in years.

M = male. F = female.

5 Medication is pseudoephedrine 60 mg and
acetaminophen 1000 mg, given once, after one
episode of a migraine attack.

Photo = photophobia.

Phono = phonophobia.

Nausea

10 Pseudoephedrine has been shown to be effective in
treating migraine patient's cardiovascular
abnormalities. A study was done on cardiovascular
reflex response in migraine patients. (Munari L,
Milaneri I, Silvani A, Bussone G, Bioardi A.
Pharmacologic evaluation of cardiovascular reflex
15 responses in migraine patients: lack of central
sympathetic modulation. *Funct. Neurol.* 1989; 4(4):375-
378.) Pretreatment with 2 mg/kg abolished the effects
of lower blood pressure after sustained handgrip that is
seen in migraine patients versus normal patients. This
20 was statistically significant data ($p < 0.05$).
Pretreatment with 2 mg/kg abolished effects of increased
postural hypotension that is seen in migraine patients
versus normal patients. This was statistically
significant data ($p < 0.05$).

25 The components of this medication are relatively
safe and with few side effects. Each component of this
medication has been available as an over-the-counter

medication in the US for other uses than the scope of this invention.

5 The uses of the combination pseudoephedrine and acetaminophen have included treatment of the symptoms associated with common cold, nasal congestion, sinus congestion, and sinus pain symptoms, but not migraine symptoms. Some examples of the brand names of these types of medication are Sudafed® Sinus Maximum, Alka-Seltzer® Plus Cold-Sinus Medicine Liqui-Gels, Infants' Tylenol® Cold Decongestant & Fever Reducer, and Excedrin® Sinus.

10 Acetaminophen has been widely used since the 1950s. Acetaminophen has been used alone for arthralgia, dental pain, dysmenorrhea, fever, headache, mild pain, myalgia, and osteoarthritis. Although, acetaminophen has been used for migraine pain, it has not been used in combination with pseudoephedrine or pseudoephedrine and caffeine. Acetaminophen has proven to be safe and with very few side effects compared to the group of NSAID analgesics. (Clissold SP., Paracetamol and phenacetin. Drugs 1986; 32 Suppl 4:315-321.)

15 Also, pseudoephedrine has been widely used and shown to be safe and with few side effects. Pseudoephedrine has been mainly used to treat nasal congestion. (Hughes DTD, Empey DW, Land M. Effects of pseudoephedrine in man. Journal of Clinical and Hospital Pharmacy 1983; 8:315-321.)

25 Caffeine is widely consumed and has also been indicated for use to treat asthma, drowsiness, fatigue, lumbar puncture headache, and neonatal apnea.

30

The length of time that acetaminophen, pseudoephedrine, and caffeine have been on the market with relatively few side effects has demonstrated their excellent safety profiles.

5 The present invention is the medicinal composition for treatment of migraine complex symptoms. The medicinal composition is an oral medication of pseudoephedrine and acetaminophen, or pseudoephedrine, acetaminophen, and caffeine. Such oral formulations
10 would be in a liquid, solid, or gelatin (semi-solid) form such as an elixir, pill, or capsule. Without limiting the scope of the present invention, an oral dosage of the combination medication may, for example, compromise;

15 Example 1) A single solid or liquid dosage form comprise of pseudoephedrine in an amount of from about 30 mg to about 60 mg, acetaminophen in an amount of from about 200 mg to about 1000 mg, and caffeine in an amount of about 40 mg to about 100
20 mg; or

 Example 2) A single solid or liquid dosage form comprise of pseudoephedrine in an amount of from about 30 mg to about 60 mg, and acetaminophen in an amount of from about 200 mg to about 1000 mg.

25 The dosage specified in Examples 1 and 2 can be taken every 6 hours by mouth. This dosage is in agreement with the over-the-counter recommended dosages of the pseudoephedrine, acetaminophen, and caffeine.

 Without limiting the scope of the present
30 invention, in the composition of these vehicles to

administrate the active medications of pseudoephedrine and acetaminophen, and pseudoephedrine, acetaminophen, and caffeine, acceptable additives may be added if desired. The acceptable additives may be in the group of glidants, lubricants, disintegrating agents, coloring agents, and fillers. Examples of these acceptable additives are pregelatinized starch, magnesium stearate, microcrystalline cellulose, croscarmellose sodium, D&C yellow #10, and colloidal silicon dioxide.

10 In conclusion, the present invention relates generally to compositions and methods used to alleviate the symptoms and pain associated with acute migraine attacks. More particularly, the present invention relates to the use of a combination of pseudoephedrine and acetaminophen with optional caffeine, and is orally administered for treating individuals afflicted with pre-migraine conditions, migraine-associated symptoms, and/or migraine pain of mild to severe intensity. The combination pseudoephedrine and acetaminophen with optional caffeine is a new, effective, and convenient medication to treat acute migraine attacks. Each of the ingredients of this combination has been shown to be useful in treating the migraine complex. Evidence shows that the ingredients of the medicinal combination work synergistically to treat migraine.

While preferred embodiments of the present invention have been disclosed, it will be appreciated that it is not limited thereto but may be otherwise embodied with the scope of the following claims.